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14. ABSTRACT

This research proposal has two primary objectives which are to (1) increase FIU investigators' research expertise and competitive ability to succeed as independent breast cancer researchers; and (2) to execute research with the promise of identifying molecular causes of breast tumor resistance to anti-estrogen therapy. This research is of significant merit because of its clinical relevance to breast cancer. Secondly, the research accomplishments through the FIU/BFBCI training program will lead to FIU investigator publication(s) in peer-reviewed journals that will facilitate the further advancement of the FIU investigators. We proposed to investigate how reactive oxygen species (ROS)-induced redox signaling pathways in breast cancer cells may contribute to molecular mechanisms of antiestrogen resistance. Our hypothesis is that the conversion of breast tumors to a tamoxifen-resistant phenotype is associated with a progressive shift towards a pro-oxidant environment of cells as a result of oxidative stress. We postulate that excess ROS levels induce both CDC25A and change p27 phosphorylation promoting the loss of its inhibitory function and leading to antiestrogen resistance. We will investigate whether reducing the oxidative environment of breast cancer cells will restore the anti-proliferative action of tamoxifen and other antiestrogens by repressing CDC25A and altering p27 phosphorylation and restoring p27 function.

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INTRODUCTION

This research proposal has two primary objectives which are to (1) increase FIU investigators' research expertise and competitive ability to succeed as independent breast cancer researchers; and (2) to execute research with the promise of identifying molecular causes of breast tumor resistance to anti-estrogen therapy. We proposed to investigate how reactive oxygen species (ROS)-induced redox signaling pathways in breast cancer cells may contribute to molecular mechanisms of antiestrogen resistance. Our hypothesis is that the conversion of breast tumors to a tamoxifen-resistant phenotype is associated with a progressive shift towards a pro-oxidant environment of cells as a result of oxidative stress. We postulate that excess ROS levels induce both CDC25A and change p27 phosphorylation promoting the loss of its inhibitory function and leading to antiestrogen resistance. We will investigate whether reducing the oxidative environment of breast cancer cells will restore the anti-proliferative action of tamoxifen and other antiestrogens by repressing *CDC25A* and altering p27 phosphorylation and restoring p27 function.

BODY

The training tasks and their progress:

To extend and enhance the FIU investigators' skills to increase their research expertise and competitive ability to succeed as independent breast cancer researchers, we proposed to conduct the following training tasks each year during the 4yr period of this project: i) To conduct onsite weekly lab meetings in which FIU investigators and trainees report research data, trouble-shoot, and plan experiments; ii) To meet every other week onsite to facilitate coordination of the project; iii) To participate in the monthly BFBCI Scientist Seminars at the University of Miami to broaden FIU investigators knowledge of the most current clinical research in breast cancer; iv) To establish an Invited Expert Breast Cancer Research Seminar Series at the FIU campus. v) To promote breast cancer research at the FIU campus, FIU/BFBCI training program will sponsor an annual onsite Breast Cancer Workshop. vi) To participate in the grant writing workshop entitled "The Molecular Mechanisms of Breast Cancer"; and vii) To prepare a written quarterly progress report of ongoing activities, and compile them together to prepare the annual progress report.

In order to meet the objective of training **Task 1**, we have been holding weekly lab meetings on every Monday at 9:30 am at the FIU campus in HLS bldg Rm 596. Since the start date of this grant, both pre-doctoral students and faculty have participated in the weekly lab meetings in which we report the results and from the interpretation of the data we plan experiments for the upcoming week. We have continued to meet since the last annual progress report date. To achieve **Task 2**, all three FIU investigators have been involved in biweekly discussions to facilitate the forward progress of this proposal at FIU. To achieve **Task 3**, all three FIU investigators and three pre-doctoral student trainees have participated in BFBCI Scientist Seminars at the University of Miami since June 2007. Drs. Roy and Felty as well as pre-doctoral student Rosalind Penny have presented results of their research during the 2008-2009 Braman Research Group Meetings. Dr. Jai Parkash and pre-doctoral student Aisha Garba are scheduled to present their research in the Fall Semester. To achieve **Task 4,** Drs. Felty and Roy have started the FIU Breast Cancer Seminar Series. Our first talk was by:

Dr. Tevik Dorak from the HUMIGEN LLC, The Institute for Genetic Immunology,Genomic Immunoepidemiology Laboratory, 2439 Kuser Road, Hamilton, NJ 08690**;** Title of Talk: Is Cancer a Ferrotoxic Disease?

Dr. Shuk-mei Ho, Professor and Chair of the Dept. of Environmental Health at the University of Cincinnati. Title of Talk: Emerging Epigenetic Issues and Hormonal Cancer.

Dr. Sushanta Banerjee, Director of Cancer Research Unit, VA Hospital Kansas City; and Professor in the Division of Hematology and Oncology at the Kansas University Medical School. Title of Talk: " CCN5 signaling in Regulation of microenvironment of Breast Cancer".

To achieve **Task 5**, we have continued to hold the Annual Breast Cancer Symposium. The first symposium was held on July 23, 2008 at the FIU campus GC Bldg. Rm 243. The symposium was highly successful with over 15 posters and presentations from FIU graduate students and faculty as well as participants from Florida Atlantic University and 44 attendees. Our guest speaker Dr. Linda Malkas is the Vera Bradley Chair of Oncology and

Professor in the Dept. of Medicine at Indiana University. She did an outstanding job with her presentation titled: "Cancer Biomarkers & Target Discovery". This symposium provided the first ever opportunity for FIU faculty and graduate students from different disciplines (i.e. Biomedical Engineering, School of Social Work, etc) to meet and establish future collaborations. We have scheduled the 2nd symposium for June 25, 2009. As part of training **Task 6**, one of our FIU faculty participated in the NIH grant training workshop. For training **Task 7** we continue to collect records of our activities in MS PowerPoint files which we use to prepare the annual report.

Challenges: One of our pre-doctoral trainees, Michelle Nyguen, who joined us in August 2007 has made the decision to pursue her Master's degree. We are currently searching for an appropriate pre-doctoral student to fill this vacancy.

In summary, we have continued all training tasks we proposed to carry out in year 2. All tasks have been fully performed and we will continue to maintain this activity throughout the time period of this award.

Research Purpose and Scope: We proposed to investigate how reactive oxygen species (ROS)-induced redox signaling pathways in breast cancer cells may contribute to molecular mechanisms of antiestrogen resistance. Our **hypothesis** is that the conversion of breast tumors to a tamoxifen-resistant phenotype is associated with a progressive shift towards a pro-oxidant environment of cells as a result of oxidative stress. We postulate that excess ROS levels induce both *CDC25A* and change p27 phosphorylation promoting the loss of its inhibitory function and leading to antiestrogen resistance. We will investigate whether reducing the oxidative environment of breast cancer cells will restore the anti-proliferative action of tamoxifen and other antiestrogens by repressing *CDC25A* and altering p27 phosphorylation and restoring p27 function.

Tasks to be accomplished in months 12-24 of this project were:

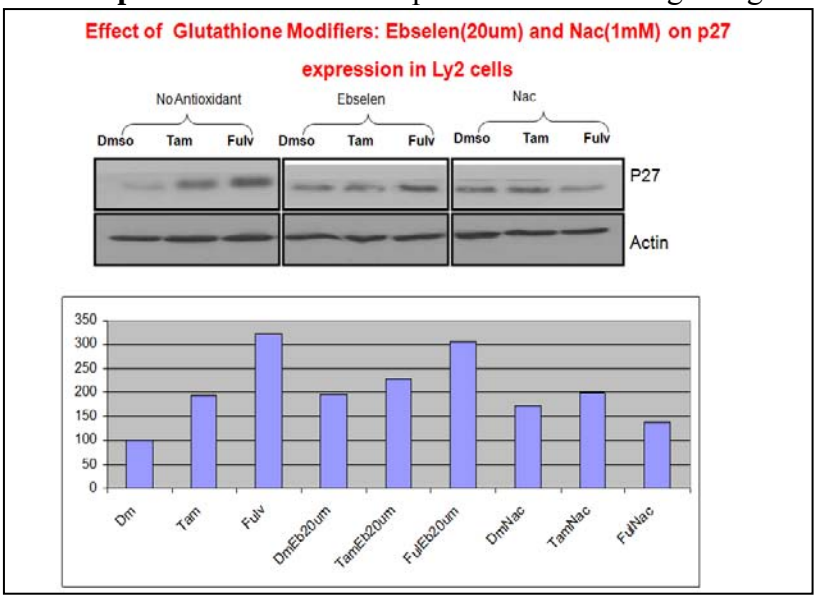
Task 1 (Months 1-24): The following tasks are a continuation of experiments in year 1.

i) To test whether the ER+ antiestrogen resistant MCF-7^R, LY-2 and LCC-2 breast cancer cell lines regain sensitivity to the inhibitory growth effects of antiestrogen when oxidant levels are reduced by (b) raised or restored levels of GSH by glutathione modifiers or overexpressing GSH restoring enzymes; and (c) raised or restored levels of Trx by thioredoxin modifiers or overexpressing Trxn. To confirm and repeat the preliminary results it would require about 6 months.

Results for Task 1 (i) Subaim (b)

The purpose of this experiment was to determine the effect of glutathione modifiers on antiestrogen exposed breast cancer cells by looking at p27 expression and p27 phosphorylation.

Anticipated Results: It is expected that redox signaling inhibition by pharmacological and genetic approaches restores the cell cycle inhibitory function of p27, reduces phosphorylation and enhances sensitivity of resistant breast cancer tumor cells to tamoxifen or fulvestrant. These studies would confirm that adaptation to higher oxidative state in breast carcinoma is not only causally linked to antiestrogen therapy resistance, but also elucidate the mechanism thereof.

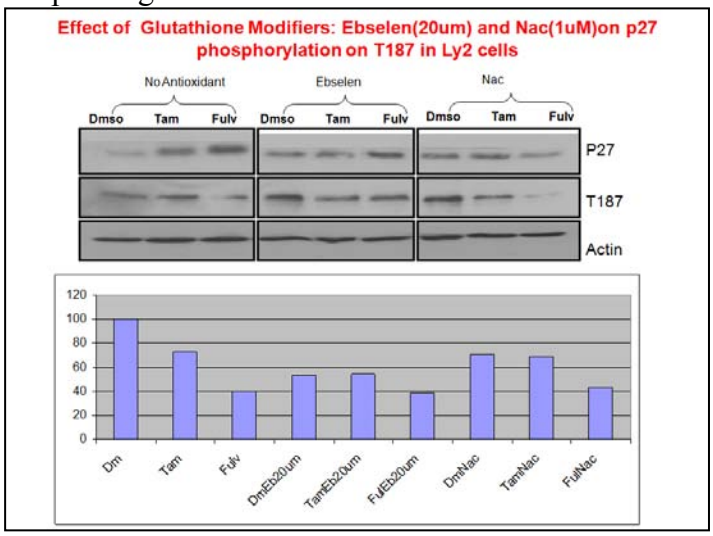


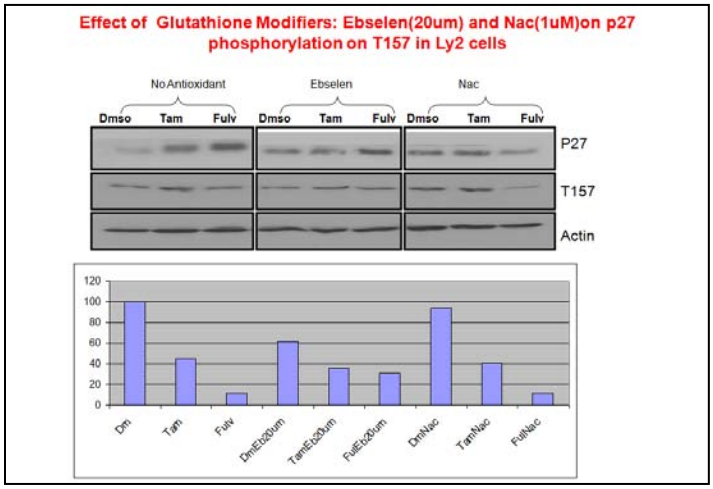
Results:

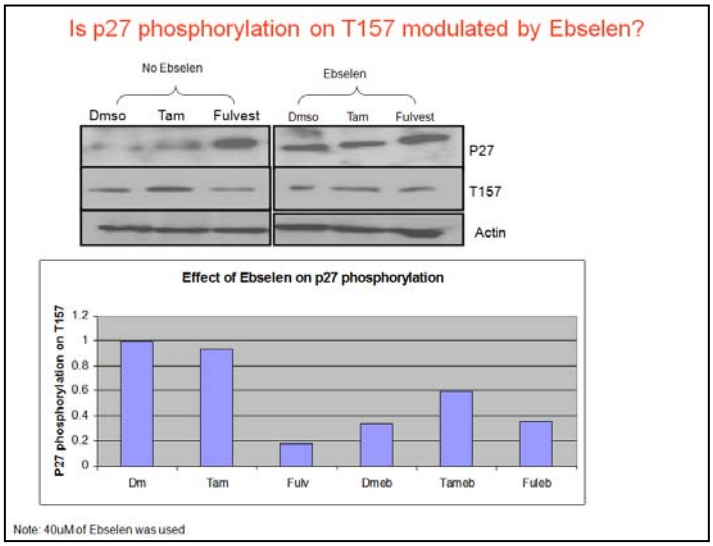
We determined the effect of GSH modifiers N-acetylcysteine (NAC) and Ebselen on the protein level of p27 in LY2 (Tamoxifen resistant) breast cancer cells exposed to antiestrogens. As shown in **Fig.** , tamoxifen exposed LY2 cells overexpressing catalase showed an increase in the p27 level. Both NAC and Ebselen showed a change in p27 levels compared to control. This data supports the overall hypothesis because it shows that p27 levels are restored when exposed to tamoxifen. Thus, the

increase in p27 levels suggest that by decreasing the oxidant state of antiestrogen resistant breast cancer cells restores redox signaling of p27 by tamoxifen. The increase in p27 levels most likely will inhibit cyclin dependent kinase activity and ultimately contribute to the suppression of the cell cycle.

Since the activity of p27 is regulated by degradation, we determined the effect of GSH modifiers NAC and Ebselen on phosphorylation of p27 at threonine-187. Threonine 187 phosphorylation is known to target p27 for proteolytic degradation. **The purpose of these experiments** was determine the effects of NAC and Ebselen had on p27 degradation via Thr 187.







Anticipated Results: We expect to see a decrease in Thr 187 phosphorylation of p27 in cells exposed to NAC and Ebselen.

Results: As shown in **Fig. ?**?, Threonine-187 levels decreased from tamoxifen exposure in LY2 cells treated with Ebselen and NAC. This correlates with the increase in p27 levels we observed in LY2 cells that regain their sensitivity to tamoxifen. The decrease in Thr-187 implies that reducing the oxidant state of the cell prevents Thr-187 targeted degradation of p27. This increases the levels of p27 in LY2 cells exposed to tamoxifen which in turn inhibits cell cycle progression. These data partly explain the regained antiestrogen sensitivity of LY2 cells to tamoxifen via redox signaling that mediate post-translational modifications of p27 which contribute to its stability.

It is known that Akt phosphorylates Thr 157 of p27 and this reduces the nuclear import activity of p27. If p27 is not in the nucleus, then it cannot inhibit G1 regulators of the cell cycle. **The purpose of this experiment** was to determine the effects of GSH modifiers had on Thr-157 of p27.

Anticipated Results: We expect that Thr-157 would either decrease or remain the same in LY2 cells exposed to GSH modifier Ebselen plus tamoxifen.

Results: As shown in **Fig. ??**, when comparing Ebselen treated LY2 cells to control there is a decrease in Thr 157 from tamoxifen exposure. The decrease in Thr-157 implies that p27 is more likely to be imported into the nucleus where it will act to inhibit cyclin dependent kinases contributing to inhibition of the cell cycle. This increase in nuclear p27 import would be in line with our hypothesis and support our colony assay data; showing that antiestrogen resistant LY2 cells are inhibited by tamoxifen when exposed to ROS modifiers that reduce the oxidant state of the cell.

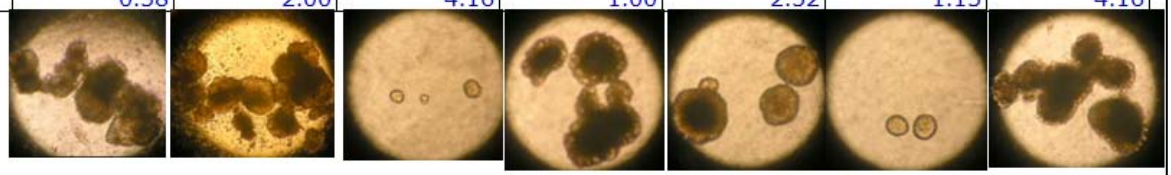
Results for Task 1 (i) Subaim (c)

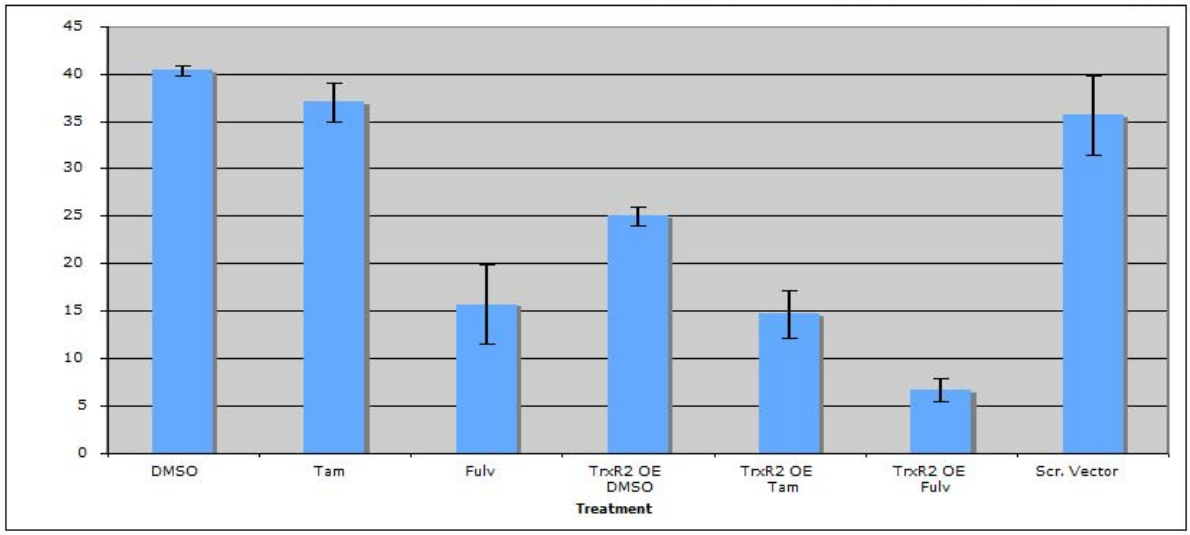
- **The purpose of this experiment** was to explore the role of thioredoxin reductase 2 (TrxR2) on tamoxifen resistant cells. Our hypothesis involves the role of reactive oxidative species (ROS) in tamoxifen resistance in breast cancer, and thus we are altering the oxidative state of tamoxifen resistant breast cancer cells through increasing the expression of TrxR2. This, in turn reduces the antioxidant thioredoxin 2 to its active form. We want to show that an increase in reduced mitochondrial thioredoxin, through the overexpression of TrxR2, will restore the growth-inhibitory actions of tamoxifen in LCC2 (tamoxifen resistant) breast cance cells, and thus decrease colony growth in soft agar.

Anticipated Results: While LCC2 cells normally grow tumors in soft agar in the presence of tamoxifen, we would expect that the overexpression of ROS modifier TrxR2 would cause tamoxifen to regain its growth inhibitory effects in this antiestrogen resistant cell line.

TrxR2 Overexpression - Soft Agar

LCC-2 cells							
TrxR2 OX							
Soft Agar Day 23							
12-Mar-09	DMSO	Tam	Fulv	TrxR2 OE DMS	TrxR2 OE Tam	TrxR2 OE Fulv	Scr. Vector
plate 1	40	35	11	25	17	6	37
	40	37	19	24	12	6	31
	41	39	17	26	15	8	39
mean	40	37	16	25	15	7	36
Std. Dev.	0.58	2.00	4.16	1.00	2.52	1.15	4.16





As shown here in **Fig. 1** (Representative photo from three independent experiments); we see a consistent reduction in LCC2 colony growth in cells overexpressing. Conclusions from this experiment is that ROS generated from tamoxifen treatment is necessary for the growth inhibition of antiestrogen sensitive breast cancer cells. The data in Fig. 1 supports our hypothesis because the manipulation of the oxidant state of antiestrogen resistant cells, increased their sensitivity to the growth inhibitory effects of tamoxifen. Thus, it appears that antiestrogen resistant breast cancer cells have adapted to a higher level of oxidant stress which can be reversed by the overexpression of thioredoxin.

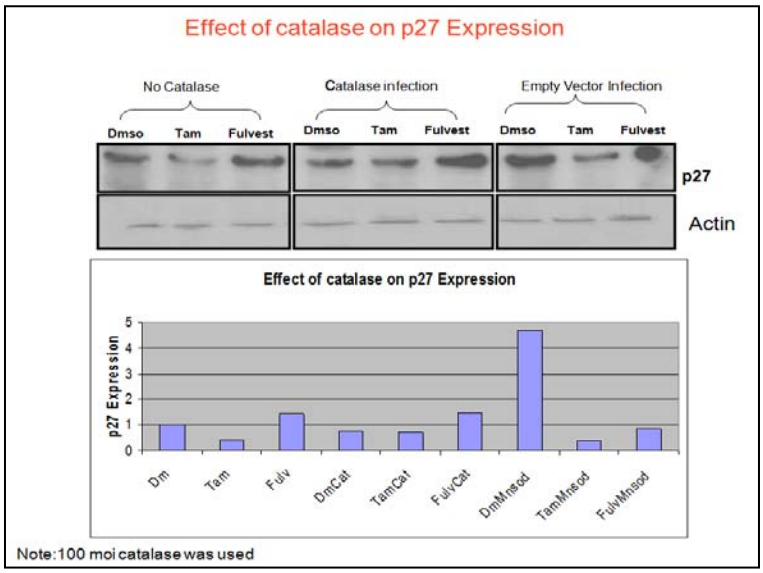
Task 1 (iii) Subaims a-f: (Months 13-24)

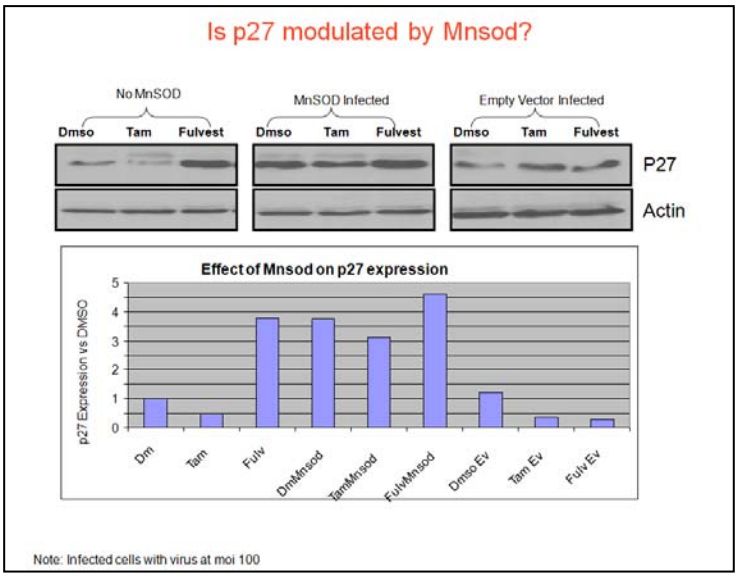
1. To determine which cell cycle regulators are critical to cell cycle effects of redox manipulations, after cell treatments with ROS modifiers and antiestrogen.

Results for Task 1 (iii) Subaim (a)

- **The purpose of this experiment** was to determine the effect of ROS modifiers on antiestrogen exposed breast cancer cells by looking at G1 regulators by RT-PCR (*c-MYC, Cyclin D1* and the Cdk2 activating phosphatase, *CDC25A*) and western analysis (cyclins E, D and A, Cdk2, 4 and 6, and p21 and p27).

Anticipated Results: It is expected that redox signaling inhibition by pharmacological and genetic approaches restores the cell cycle inhibitory function of p27, reduces CDC25A expression and enhances sensitivity of resistant breast cancer tumor cells to tamoxifen or fulvestrant. These studies would confirm that adaptation to higher oxidative state in breast carcinoma is not only causally linked to antiestrogen therapy resistance, but also elucidate the mechanism thereof.



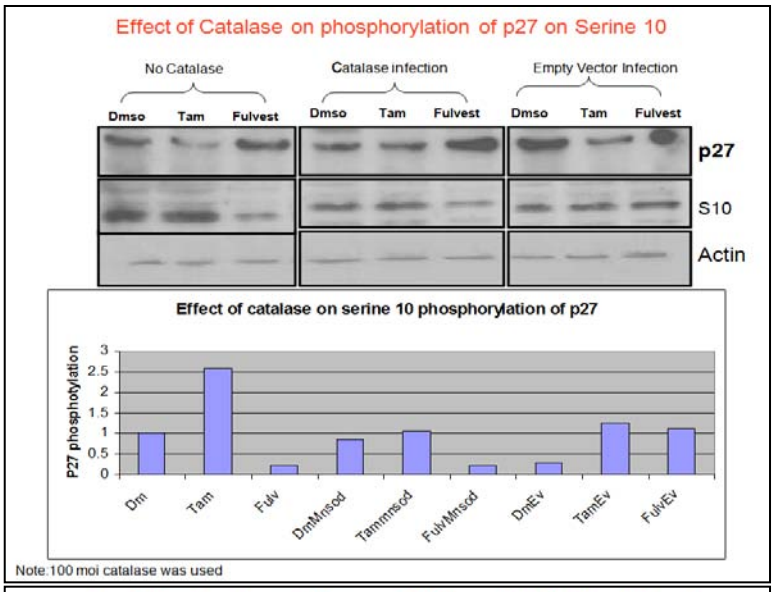


Results:

We first determined the effect of ROS modifiers catalase and MnSOD had on the protein level of p27 in LCC2 (Tamoxifen resistant) breast cancer cells exposed to antiestrogens. As shown in **Fig.** , tamoxifen exposed LCC2 cells overexpressing catalase showed an increase in the p27 level. Overexpression of MnSOD showed a more pronounced increase in p27 levels compared to control. This data supports the overall hypothesis because it shows that p27 levels are restored when exposed to tamoxifen. Thus, the increase in p27 levels suggest that by decreasing the oxidant state of antiestrogen resistant breast cancer cells restores redox signaling of p27 by tamoxifen. The increase in p27 levels most likely will inhibit cyclin dependent kinase activity and ultimately contribute to the suppression of the cell cycle.

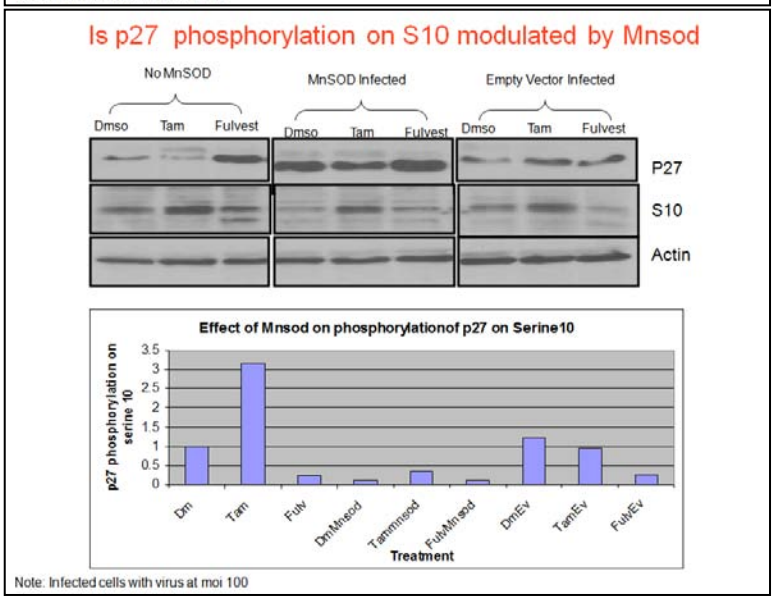
We have yet to complete the RT-PCR of cell cycle genes. We could not complete this task because one of our pre-doctoral students changed from the PhD to MPH program. We have overcome challenge this by hiring a Post-Doc (Dr. Alok Deoraj) in place of her.

p27 associates with cyclin and cyclin-dependent kinase complexes to inhibit their kinase activity and contribute to the control of cell proliferation. p27 is phosphorylated on many sites, including threonine 187, in vivo , with the predominant phosphorylation site being serine 10. The extent of serine 10 phosphorylation by proline-directed kinase is markedly increased in cells in the G0-G1 phase of the cell cycle compared to cells in the S or M phase. Therefore **the purpose of these experiments** was to determine whether the phosphorylation of p27 was being modulated by overexpressing catalase (an H2O2 scavenger) and MnSOD (a superoxide radical scavenger).

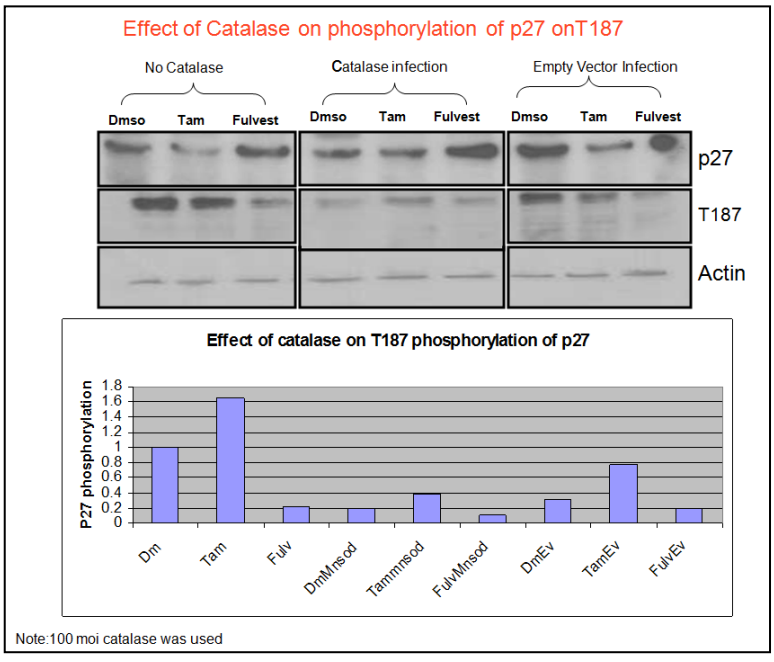


Anticipated Results: We expect to see an increase in Serine 10 phosphorylation in cells overexpressing catalase and/or MnSOD.

Results: As shown in **Fig. ??**, both catalase and MnSOD overexpressing LCC2 cells (Tamoxifen resistant) show an increase in Ser 10 phosphorylation when exposed to tamoxifen. Since Ser 10 phosphorylation is known to increase the protein stability of p27, this data supports our previous findings that p27 levels are increased reversing the antiestrogen resistance of LCC2 cells. Our data supports our hypothesis because an increase in Ser 10 of p27 would stabilize p27 protein resulting in an increase in p27 levels that would account for the regained sensitivity of antiestrogen resistant LCC2 cells have to Tamoxifen.

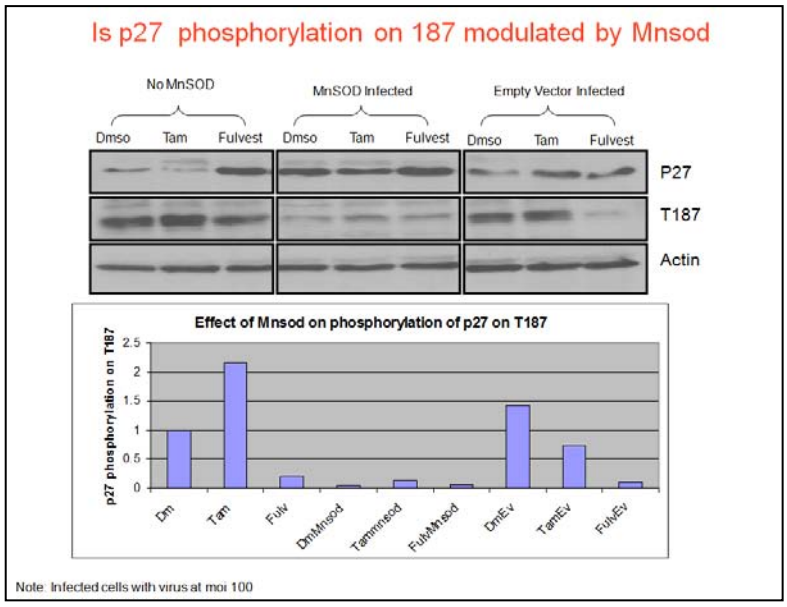


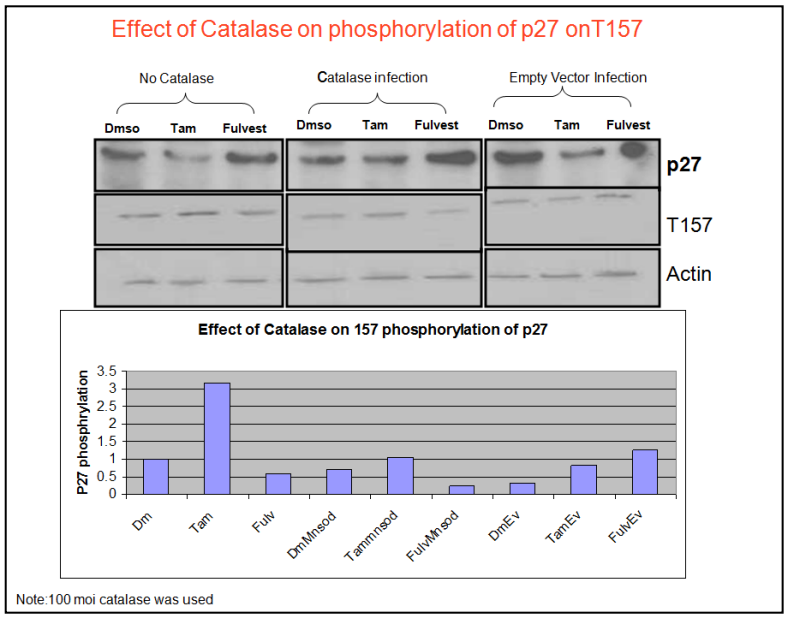
Since the activity of p27 is regulated by degradation, we determined the effect of CAT and MnSOD overexpression had on phosphorylation of p27 at threonine-187. Threonine 187 phosphorylation is known to target p27 for proteolytic degradation. **The purpose of these experiments** was determine the effects of CAT and MnSOD overexpression had on p27 degradation via Thr 187.

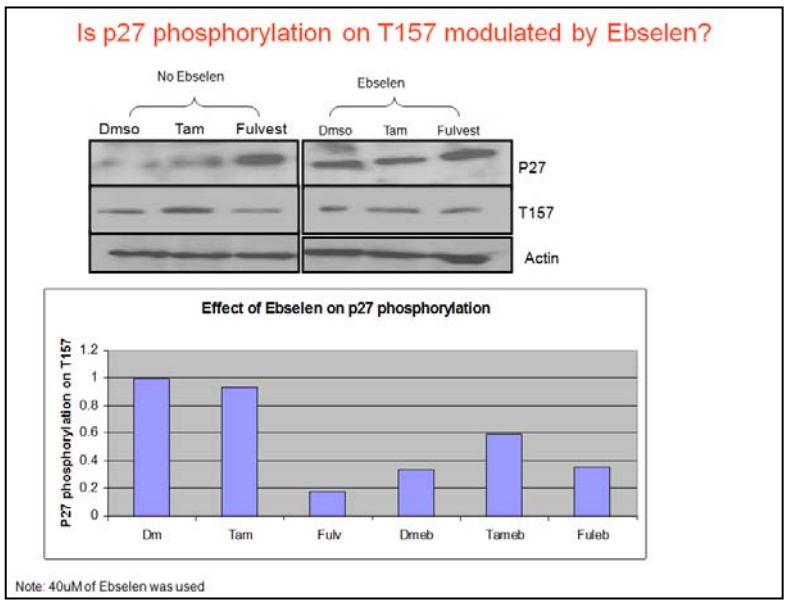


Anticipated Results: We expect to see a decrease in Thr 187 phosphorylation of p27 in cells overexpressing CAT and/or MnSOD.

Results: As shown in **Fig. ??**, Threonine-187 levels decreased from tamoxifen exposure in LCC2 cells overexpressing CAT. This correlates with the increase in p27 levels we observed in LCC2 cells that regain their sensitivity to tamoxifen. The decrease in Thr-187 implies that reducing the oxidant state of the cell prevents Thr-187 targeted degradation of p27. This increases the levels of p27 in LCC2 cells exposed to







tamoxifen which in turn inhibits cell cycle progression. In addition, we observed a similar decrease in Thr-187 in the LCC2 cells overexpressing MnSOD (**Fig. ??**). Together these results are consistent with our previous data showing an increase of p27 in tamoxifen exposed LCC2 cells overexpressing antioxidant enzymes catalase (CAT) and MnSOD. These data partly explain the regained antiestrogen sensitivity of LCC2 cells to tamoxifen via redox signaling that mediate post-translational modifications of p27 which contribute to its stability.

It is known that Akt phosphorylates Thr 157 of p27 and this reduces the nuclear import activity of p27. If p27 is not in the nucleus, then it cannot inhibit G1 regulators of the cell cycle. **The purpose of this experiment** was to determine the effects of ROS modifiers had on Thr-157 of p27.

Anticipated Results: We expect that Thr-157 would either decrease or remain the same in LCC2 cells overexpressing CAT and/or MnSOD when exposed to tamoxifen.

Results: As shown in **Fig. ??**, when comparing CAT overexpressing LCC2 cells to the vector control there is no change in Thr 157 from tamoxifen exposure. However, we did show a decrease in Thr-157 of p27 when LCC2 cells were exposed to the chemical antioxidant ebselen. The decrease in Thr-157 implies that p27 is more likely to be imported into the nucleus where it will act to inhibit cyclin dependent kinases contributing to inhibition of the cell cycle. This increase in nuclear p27 import would be in line with our hypothesis and support our colony assay data; showing that antiestrogen resistant LCC2 cells are inhibited by tamoxifen when exposed to ROS modifiers that reduce the oxidant state of the cell.

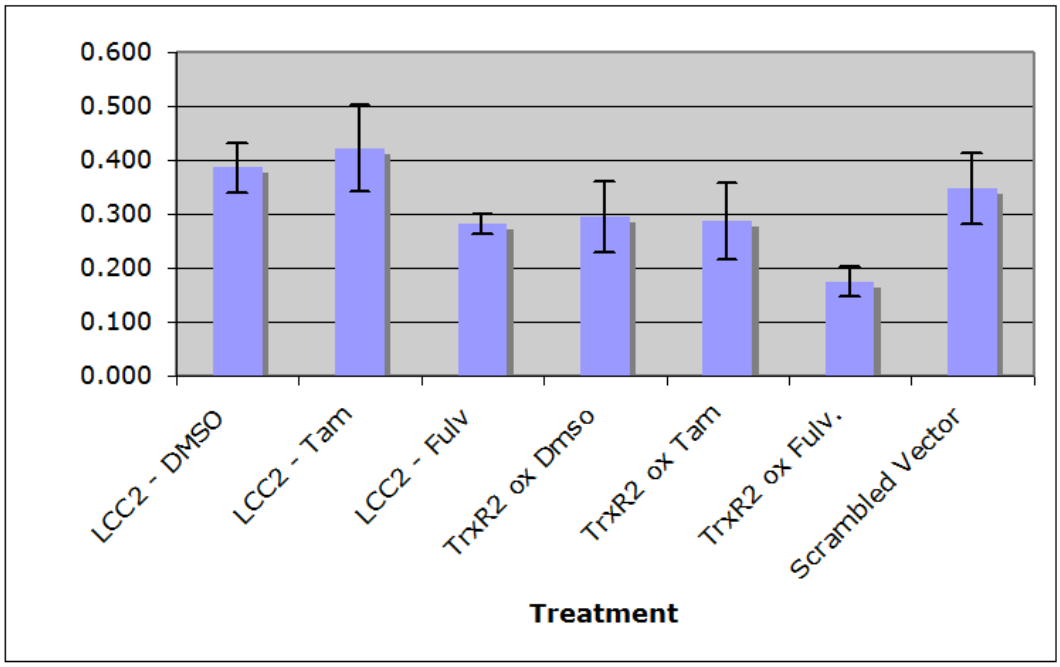
Results for Task 1 (iii) Subaim (c): We will also assay the cell cycle profile by flow cytometry after BrdU pulse labeling and propodium iodide staining.

- **The purpose of this experiment** was to explore the role of TrxR2 on DNA synthesis of tamoxifen resistant cells. As with the previous experiment, we are altering the oxidative state of tamoxifen resistant breast cancer cells through increasing the expression of TrxR2. This, in turn reduces the antioxidant thioredoxin 2 to its active form, and reduces the oxidative state of the cells.

Anticipated: Since tamoxifen is known to increase the oxidative state of breast cancer cells, an increase in reduced mitochondrial thioredoxin, through the overexpression of thioredoxin reductase 2, should restore the growth-inhibitory actions of tamoxifen in LCC2 (tamoxifen resistant) breast cancer cells, and thus decrease DNA synthesis.

TrxR2 Overexpression - BrdU

	LCC2 - DMSO	LCC2 - Tam	LCC2 - Fulv	TrxR2 ox Dmso	TrxR2 ox Tam	TrxR2 ox Fulv.	Scrambled Vector
10 min	0.442	0.498	0.306	0.235	0.197	0.186	0.421
	0.401	0.43	0.267	0.36	0.344	0.165	0.262
	0.347	0.449	0.281	0.338	0.34	0.14	0.356
	0.351	0.311	0.269	0.239	0.26	0.204	0.348
mean	0.385	0.422	0.281	0.293	0.285	0.174	0.347
Std Dev.	0.045	0.079	0.018	0.065	0.070	0.028	0.065
% change	100	110	73	76	74	45	90



As shown in **Fig. ??**, the antiestrogen resistant LCC2 breast cancer cells normally grow in the presence of tamoxifen, however, in cells overexpressing TrxR2 we observed the LCC2 cells to regain their sensitivity to the growth inhibitory effects of tamoxifen. There was a 33% decrease in DNA synthesis in TrxR2 overexpressing cells exposed to tamoxifen indicating that when the oxidative state of tamoxifen resistant cells is reduced, the tamoxifen inhibits DNA synthesis.

CHALLENGES AND DIFFICULTIES ENCOUNTERED.

Task 1 (iii) the following subaims b, d, e, f have not been completed

(b) We will assay cyclin-Cdk complexes for activity and associated Cdk2 inhibitors, p27 and p21.
(d) p27 phosphorylation will be assayed by 2D-phosphopeptide mapping.
(e) The roles of putative redox responsive p27 phosphorylation sites will be investigated using phosphomutant p27 alleles.
(f) p27's assembly function for cyclin D1-cdk4 or reduced ability to bind and inhibit cyclin E-cdk2 will also be assayed.

Task 2 (Months 13-24): have not been completed
2. To test whether persistant oxidant generation abrogates antiestrogen action in sensitive cells through effects on cell cycle regulators and in particular on p27. *In order to complete this task, we need to address following questions (Months 24-36):*

i) To test if pro-oxidative manipulations increase G1 progression, stimulate a more rapid cell cycle proliferation by increasing the levels and activities of G1 cyclin E and A-Cdk2, and of the Cdk2 activating phosphatase, Cdc25A and by promoting degradation of the Cdk2 inhibitors, p21 and p27 or their mislocalization in the cytoplasm.
ii) To determine that these cells treated with pro-oxidant plus antiestrogen if they have become resistant to antiestrogen-mediated G1 arrest can be modified by concurrent treatment with ROS inhibitors. a) To analyze the expression of G1 genes (*c-MYC*, *Cyclin D1* and *CDC25A*) by real time RT-PCR, and assay cyclins D, E and A, their Cdk levels and cyclin-Cdk-Cdk inhibitor complexes and kinase activities in addition to cell cycle profile by flow cytometry. b) To assay the phosphorylation, immunolocalization of p27 and its Cdk2 inhibitory function after the redox manipulations with or without antiestrogens.

Training: Two of our pre-doctoral trainees are progressing satisfactorily while one trainee has had difficulty with both didactic coursework as well as research performance. We could not complete some of the tasks because one of our pre-doctoral students changed from the PhD to MPH program. We have overcome the challenge by hiring a Post-Doc (Dr. Alok Deoraj) in place of her.

Research: Even though most of the research techniques are routinely performed in the PI's and Co-PI's laboratories at FIU, the pre-doctoral trainees need to become familiar with these techniques and standardize them. However, finding a post-doc took several months. And once hired it takes time to orient the post-doc to the research project. Furthermore, mastering new techniques can take time for a pre-doctoral student, which has slowed down progress on measuring cyclin complex activity and 2D phosphopeptide mapping. However, we have overcome these difficulties and we are working at full capacity to complete the research proposed in Year 2. Still the MCF-7R cell line is not available from Dr. Slingerland's lab due to fungal infection so we have only reported progress using two antiestrogen resistant cells LY-2 and LCC-2. The lack of progress from one of the pre-doctoral trainees has also slowed down research accomplishments, but we have overcome this by hiring a new post-doc as described in the training section.

KEY RESEARCH ACCOMPLISHMENTS

- Showed that overexpression of ROS modifiers Trx, Catalase, MnSOD in the Tamoxifen resistant breast cancer cell line LCC2 restored sensitivity to growth inhibition by tamoxifen.
- Showed that the mechanism of regained antiestrogen sensitivity of LCC2 to tamoxifen is mediated by redox sensitive phosphorylation of p27 at Ser-10, Thr-187, and Thr-157.

REPORTABLE OUTCOMES

Publications: Two abstracts were accepted and presented at the AACR meeting held in Denver, Colorado April 18-22, 2009.

1. Felty Q. Estrogenic PCBs increase blood vessel formation by redox signaling [abstract]. In: Proceedings of the 100th Annual Meeting of the American Association for Cancer Research; 2009 Apr 18-22; Denver, CO. Philadelphia (PA): AACR; 2009. Abstract nr 4016.
2. Roy D, Felty Q, Okoh V. NRF-1 signaling participates in the estrogen-mediated growth of breast cancer cells. [abstract]. In: Proceedings of the 100th Annual Meeting of the American Association for Cancer Research; 2009 Apr 18-22; Denver, CO. Philadelphia (PA): AACR; 2009. Abstract nr 3360.

Grants Awarded:

1. Felty, Q. (Principal Investigator) 07/01/09-06/30/12
   Florida Department of Health, Bankhead-Coley Research Program NIR Award (09BN-06)
   ; Title: "Metastases and Promotion of Aggressive Angiogenic Phenotype in Breast Cancer"

CONCLUSION

These initial results show support towards our hypothesis, with increased ROS and cell proliferation in breast cancer cells upon treatment with antiestrogens, and the cotreatment with ROS modifiers restore the growth inhibitory effects of antiestrogen in resistant cells. As the overall knowledge of ROS and p27, as well as new results based on the hypothesis, is being expressed in these experiments, it is evident that further investigation into the hypothesis is necessary and justified.